REMARKS

The Invention

The invention is drawn to methods for detecting cancer of an organ in a specimen of a body fluid that drains the organ. The specimen can be urine, sputum, bile, stool, cervical smears, saliva, tears, cerebral spinal fluid, or lymph nodes. A plurality of microsatellite markers in the specimen is tested to determine a microsatellite marker length alteration in the specimen relative to a control sample. A microsatellite marker length alteration in the specimen relative to the control sample indicates the presence of a cancer in the organ that drains into the body fluid. (Claim 24.) The method can be used to detect lung cancer in a sputum specimen (claim 23), or to detect bladder cancer in a urine specimen (claim 31). The method can also be used on a blood sample (claim 38).

The invention is also drawn to a method for detecting cancer cells in a histopathological margin specimen external to a primary tumor. A plurality of microsatellite markers in a histopathological margin specimen external to a primary tumor is tested to determine a microsatellite marker length alteration relative to a control sample. A length alteration indicates the presence of cancer cells in the specimen. (Claim 34.)

The Amendments

Claim 23 has been amended to correct a perceived lack of antecedent basis. Claim 24 has been amended to remove blood from the Markush group. Claim 38, reciting blood, has been amended to become independent. In addition, it has incorporated the limitation of claim 37, *i.e.*, identifying a cancer. Claim 37 is dependent on claim 24 which formerly recited blood as a

specimen. Thus this amendment does not represent a new combination of elements. It is respectfully submitted that none of these amendments adds new matter or raises any new issues.

These amendments were not made sooner because the deficiency was not noted earlier in the case of claim 23. In the case of claims 24 and 38, their subject matter was not separated sooner because they were not previously deemed to contain both allowable and non-allowable subject matter. Separating such subject matter puts the claims in better condition for appeal or allowance.

The Rejection of Claims 24-28, and 37-38 Under 35 U.S.C. § 103 (a)

Claims 24-28, and 37-38 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Brugieres et al. (Cancer Research, Feb. 1993, vol. 53, pp 452-455) in view of Gonzalez-Zulueta (Cancer Research 1993), Merlo et al., (Cancer Research 1994), and Ah-See et al. (Cancer Research, 1994). Applicants respectfully traverse.

Each of claims 38-45 were dependent on claim 24, each reciting a different specimen mentioned in the Markush group of claim 24. Only claim 38 (reciting blood) of the group of claims 38-45, was rejected over prior art. Applicant believes that removal of "blood" from the Markush group of claim 24 thus renders claim 24 allowable over the prior art, like each of its constituent Markush elements recited in dependent claims 39-45.

Based on that belief, this discussion will focus solely on claim 38, which retains the subject matter of claim 24 with blood as the specimen. Claim 38 has been further amended to include the recitation of claim 37, *i.e.,* identifying the specimen as containing cancer cells.

To reject claims under 35 U.S.C. § 103(a), the Patent Office has the burden of establishing a *prima facie* case of obviousness. "To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." MPEP § 2143.03, citing *In re Royka*, 490 F.2d 981 (CCPA 1974). It is respectfully submitted that the combination of Brugieres et al., Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. do not teach or suggest all the limitations of properly construed claim 38.

Claim 38 recites:

> A method for detecting cancer of an organ in a specimen of a body fluid which drains the organ, wherein the specimen is blood, comprising the step of:
>
> testing a plurality of microsatellite markers in the specimen to determine a microsatellite marker length alteration relative to a control sample;
>
> ***identifying a cancer in the organ which drains into the body fluid*** if a microsatellite marker length alteration is determined in the specimen relative to the control sample.

Emphasis added. Claim 38 is drawn to a method of detecting cancer of an organ by testing a body fluid that drains the organ. The combination of Brugieres et al., Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. do not teach such a method, particularly the step of identifying a cancer in the organ which drains in the body fluid, as recited in claim 38.

Brugieres et al. teach "the results of screening for p53 germ line mutations." (Page 452, second column, line 7.) Germline mutations are found <u>in all cells</u> of an individual. Thus the mutation that Brugieres identifies is not due to the presence of a mutation in an organ that drains

into the blood. On the contrary, the mutation is found in the blood cells as well as in all other cells of the body. No tumor is present in such a case, as Brugieres screens for predisposition to cancer, not presence of a cancer. Brugieres et al. does not teach screening for p53 mutations in blood to determine the presence of a cancer in an organ which drains into the blood. Thus Brugieres et al. fails to teach identifying a cancer of an organ which drains into the body fluid as required by claim 38.

Gonzalez-Zulueta et al. also do not teach or suggest identifying cancer of an organ in a specimen of a body fluid which drains the organ. Gonzalez-Zulueta et al. teaches "that genomic instability as measured by changes in microsatellite repeats occurs in TCC of the bladder." (Page 5622, first column, lines 1-2 of the Discussion, emphasis added.) Gonzalez-Zulueta et al. teach determining microsatellite repeat polymorphisms in the bladder cancer cells. Thus Gonzalez-Zulueta et al. does not teach determining microsatellite repeat polymorphisms in a body fluid that drains an organ and identifying cancer in the organ.

Merlo et al. also do not teach identification of a cancer by determining microsatellite repeat polymorphisms in a body fluid that drains an organ. Merlo et al. teaches that "many small cell lung cancers display widespread microsatellite alteration potentially constituting a distinct RER phenotype." (Page 2098, second column, lines 9-11, emphasis added.) Thus Merlo et al. teach determining microsatellite alteration in the tumor sample, not a body fluid that drains an organ.

Ah-See et al. also do not teach identification of a cancer by determining microsatellite repeat length alterations in a body fluid that drains an organ. Ah-See et al. teach comparing

"normal and tumor DNA from 28 patients using a battery of 50 markers." (Emphasis added, page 1617, second column, lines 4-5.) Thus, Ah-See et al. teach detection of microsatellite repeat length alterations in the cells of a tumor, and not in a body fluid that drains an organ.

Brugieres et al., Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. each fail to teach identifying cancer of an organ in a specimen of a body fluid which drains the organ. Thus the combination of Brugieres et al., Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. fails to teach all the limitations of claim 38. Withdrawal of this rejection of claim 38 is respectfully requested as a *prima facie* case of obviousness has not been established.

The Rejection of 34 Under 35 U.S.C. § 103 (a)

Claim 34 is rejected under 35 U.S.C. § 103 (a) as being unpatentable over Hayashi et al. (Cancer Research, July 1994, Vol. 54, p 3853-3856), in view of Gonzalez-Zulueta (Cancer Research 1993), Merlo et al. (Cancer Research 1994), and Ah-See et al. (Cancer Research, 1994). Applicants respectfully traverse.

To reject claims under 35 U.S.C. § 103(a), the Patent Office has the burden of establishing a *prima facie* case of obviousness. "To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art." MPEP § 2143.03, citing *In re Royka*, 490 F.2d 981 (CCPA 1974). It is respectfully submitted that the combination of Hayashi et al., Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. do not teach all the limitations of properly construed claim 34.

Claim 34 as amended requires that the tested specimen be a "histopathological specimen comprising a tumor margin which is external to the primary tumor." This element of claim 34 is not taught or suggested by the combination of Hayashi et al., Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. The Patent Office asserts that this element cannot be used to differentiate claim 34 from the prior art because the "specification does not teach what is meant by the term 'histopathological margin specimen' nor does the specification define or limit the distance encompassed by the phrase 'histopathological margin specimen external to a primary tumor' (exact wording in claim) (ie: the distance from the primary tumor encompassed by the term external). (Paper 21, page 8, lines 5-9.) Therefore "the features upon which applicant relies (tumor margin) are not recited in the rejected claim(s)." (Paper 21, page 8, lines 9-10.) Applicants understand the examiner's rejection to be based on a slightly different term being used in the claim and in the specification. Thus applicants have amended claim 34 to conform to the term which is clearly defined in the specification, *i.e.*, "tumor margin."

A "histopathological specimen comprising a tumor margin which is external to the primary tumor" is definite and must be given due weight and consideration. The PTO is not free to ignore claim limitations willy-nilly. The disputed term is sufficiently clear and definite to distinguish over the cited prior art. First, according to its plain meaning, a "tumor margin which is external to the primary tumor" is a specimen that does not include the primary tumor. Second, the specification teaches,

> As used herein the term "tumor margin" refers to the tissue surrounding a discernible tumor. In the case of surgical removal of a solid tumor, the tumor margin is the tissue cut away with the discernible tumor that usually

> appears to be normal to the naked eye. More particularly, as used herein, "margin" refers to the edge, border, or boundary of a tumor. The margin generally extends from about 0.2 cm to about 3 cm from the primary tumor but can be greater depending upon the size of the primary solid tumor.

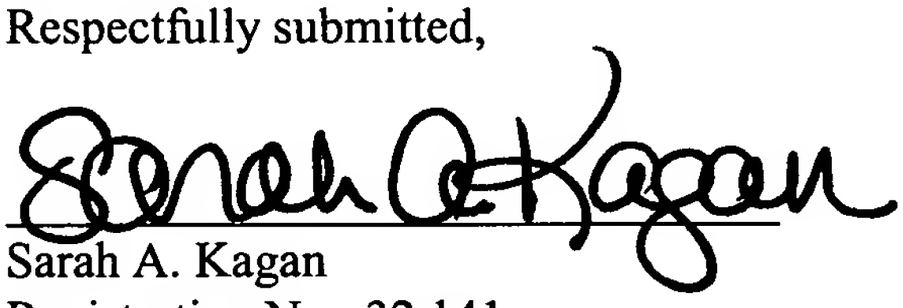
(Page 9, lines 15-18.) Thus the "specimen comprising a tumor margin which is external to the primary tumor" is tissue that surrounds the discernible tumor and that is typically cut away with the discernible tumor, *i.e.,* of the same tissue as the tumor. None of Hayashi et al., Gonzalez-Zulueta et al., Merlo et al., nor Ah-See et al. teach or suggest testing such a tumor margin specimen.

Hayashi et al. screened "22 colorectal cancers for K-ras and p53 mutations and examined corresponding regional lymph node at the genetic level by the MASA [mutant allele-specific amplification] method." (Page 3853, first column, lines 4-6 of the Abstract.) Thus, Hayashi et al. teach the determination of particular mutations in colorectal tumors and in lymph nodes. Tumors are, by definition, not external to a tumor. Lymph nodes are distinct organs from a colorectal tumor, thus they do not constitute a tumor margin. Hayashi et al. do not teach examination of a genetic alteration in a histopathological margin specimen that is in the same tissue or organ, as required by properly construed claim 34.

Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. also do not teach detection of microsatellite marker length alterations in a histopathological specimen comprising a tumor margin. Thus Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. do not remedy the defect of Hayashi et al. As indicated previously, Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. each teach detection of microsatellite instability directly in the cells of the tumor. The

combination of Hayashi et al., Gonzalez-Zulueta et al., Merlo et al., and Ah-See et al. do not teach or suggest the detection of microsatellite marker length alterations in a histopathological specimen comprising tumor margin. The *prima facie* case is defective because none of the references teach this element of the claim. Withdrawal of this rejection of claim 34 is respectfully requested.

Respectfully submitted,

Date: May 3, 2002 By: 

Sarah A. Kagan
Registration No. 32,141

Banner & Witcoff, Ltd.
1001 G Street, NW
Washington, DC 20001
202-508-9100

APPENDIX

23. (Thrice Amended) A method for detecting lung cancer in a sputum specimen, comprising the step of:

testing a plurality of microsatellite markers in the specimen to determine a microsatellite marker length alteration relative to a control sample, wherein a microsatellite marker length alteration in the specimen relative to the control sample indicates the presence of a cancer in a [the] lung which drains into the sputum.

24. (Thrice Amended) A method for detecting cancer of an organ in a specimen of a body fluid which drains the organ, wherein the specimen is selected from the group consisting of: [blood,] urine, sputum, bile, stool, cervical smears, saliva, tears, cerebral spinal fluid, and lymph nodes comprising the step of:

testing a plurality of microsatellite markers in the specimen to determine a microsatellite marker length alteration relative to a control sample wherein a microsatellite marker length alteration in the specimen relative to the control sample indicates the presence of a cancer in the organ which drains into the body fluid.

Not entering

34. (Twice Amended) A method for detecting cancer cells in a histopathological [margin] specimen comprising a tumor margin which is external to a primary tumor comprising the steps of:

testing a plurality of microsatellite markers in a histopathological [margin] specimen comprising a tumor margin which is external to a primary tumor to determine a microsatellite marker length alteration relative to a control sample, wherein a length alteration indicates the presence of cancer cells in the specimen.

38. (Once Amended) A [The] method [of claim 24] for detecting cancer of an organ in a specimen of a body fluid which drains the organ, wherein the specimen is blood, comprising the step of:

testing a plurality of microsatellite markers in the specimen to determine a microsatellite marker length alteration relative to a control sample;

identifying a cancer in the organ which drains into the body fluid if a microsatellite marker length alteration is determined in the specimen relative to the control sample.